REMARKS

1. Claim Objections and Rejections

Claims 1, 3, 5, 8-12, 17-24, 28 and 57-58 are currently under examination. The Examiner has indicated that most of the claim objections and indefiniteness rejections have been rendered moot or obviated in view of Applicant's prior response. The Examiner, however, has maintained the rejection of claims 1 and 12 for various informalities. Applicant has amended claim 1 to remove the reference to the non-elected SEQ ID Nos 4 and 6. Applicant would like to point out that claim 12 does not refer to SEQ ID No. 35. The reference to SEQ ID Nos. 34 and 35 was removed in Applicant's last response. Applicant submits that the foregoing claim amendments have overcome the Examiner's objection. Reconsideration and removal of the objection is respectfully requested.

2. Claim Rejections under 35 U.S.C. §112

The Examiner has again rejected claims 1, 3, 5, 8-12, 17-24, 28 and 57-58 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. The Examiner has considered and responded to the arguments presented in Applicant's prior response. The Examiner's remarks are presented in paragraphs 11-18 (particularly paragraphs 13-18) of the Office Action. Applicant respectfully traverses the rejection and Applicant's specific comments in relation to the Examiner's arguments in paragraphs 13-18 are presented below.

Applicant had previously argued that a person of ordinary skill in the art would be able to make and use the present invention based on the teachings in the Specification and the knowledge generally available in the art. Applicant's arguments, as summarized by the Examiner were as follows:

(a) peptide and polypeptide vaccination against self-proteins is well known in the art of immunology; antibodies raised against the self-protein will lead to its destruction or interfere with its function and hence result in down regulation;

(b) the Specification provides ample guidance on how a skilled artisan can mutate SEQ ID NO.2 and that the introduction of almost any mutation in SEQ ID NO. 2 will lead to an immunogenic variant or mutant capable of MHC II binding and result in the breaking of autotolerance; the function of any given OPGL or mutant thereof is not relevant;

(c) regulation and down-regulation are defined in the Specification and methods of synthesizing, screening and evaluating non-peptide analogues would only require routine experimentation; and

(d) the OPGL polypeptide analogue must have the general formula included in claim 1 and therefore does not encompass any frameshift mutations; any mutation will result in a usable mutein for practicing the invention.

The Examiner has indicated that each of these arguments was considered but found unpersuasive. As noted above, the Examiner's specific comments with respect to the alleged lack of enablement are set forth in the paragraphs numbered 13-18 of the Final Office Action. Applicant responds to each of the Examiner's comments on an item-by-item basis as follows:

i) Paragraph 13

In paragraph 13 of the Final Office Action, the Examiner has agued that it is not clear from the Specification or the prior art that immunization with SEQ ID NO. 2 will lead to the desired effect. The Examiner cites to an article by Bendayan which teaches that antibodies raised against a specific sequence are not only specific for the parent protein but can display unwanted cross-reactivity with related and unrelated proteins. Thus, the Examiner argues that constructs according to the claims could trigger rampant and non-specific breaking of autotolerance resulting in an autoimmune disease. While Applicant does not dispute the fact that an immunogen as claimed could raise cross-reactive antibodies, it should be noted that this is true for *any immunogen*, not merely for immunogens based on self-protein material. If a skilled

artisan were to accept the Examiner's position, then no vaccination would be feasible as the myriad of epitopes present in the inactivated viral particles or killed bacteria of the vaccine would cross-react or trigger a rampant and uncontrolled response. This is hardly the case as vaccination is an accepted means of preventing disease, despite the fact that adverse effects may be observed.

Moreover, Applicant would like to point out that the presently claimed vaccines are immunogenic due to the presence of a *foreign* T helper cell epitope. The prior art vaccines used a wild-type self sequence which can trigger an uncontrolled autoimmunity which can not readily be discontinued because the immune response is driven by autologous T helper epitopes. This type of uncontrolled autoimmunity would not occur in the present invention because the autoimmunity would effectively be discontinued when the administration of the vaccine is stopped. So contrary to the Examiner's argument, the present vaccines actually allow for a controlled immune response unlike the prior art vaccines which use a wild-type self sequence.

Applicant submits that a person of ordinary skill in the art would expect that immunization with the claimed constructs would lead to the down regulation of OPGL activity in the subject based on the teachings in the Specification and their own knowledge regarding the use of peptide-based vaccines. Applicant hereby submits a Declaration of Dr. Marc Hertz, which was filed in a co-pending application (serial number 09/396,937), which demonstrates that vaccination against autologous OPGL (identical to RANKL) (1) induced the OGPl immunological response and (2) is a feasible means of presenting bone loss. In view of this evidence, it is clear that a person of ordinary skill in the art would believe that there is a reasonable expectation that the claimed construct would work for its intended purpose.

ii) Paragraph 14

In paragraph 14, the Examiner acknowledges that mutations can be introduced into SEQ ID NO. 2. However, the Examiner argues that this does not guarantee that the mutation will yield a useful variant to practice the invention. Citing to an article by Jobling and Holmes, the Examiner argues that a single point mutation can destroy the antigenicity of a protein. The

Examiner further states that the Applicant has provided little or no guidance to enable the ordinary artisan, without undue experimentation, to determine the positions in the protein that are tolerant to change and the nature and extent of the changes that can be made in these positions. Applicant respectfully disagrees.

First, Applicant would like to point out that the claims require that at least one B-cell epitope of OPGL be present in the vaccine construct. Hence, the immunogen of the claim is by its very nature an immunogen whose antigenicity is intact. The present invention is directed to a polypeptide, which includes at least one preserved OPGL B-cell epitope, and at least one foreign T-helper cell epitope not to an OPGL sequence with a mutation that renders the construct immunogenic.

Second, Applicant submits that the Jobling reference does not definitively establish demonstrate that point mutations lead to an absolute loss of immunoreactivity. The Jobling reference only teaches that a recombinant cell may produce less of a given protein, when the DNA encoding it has been mutated. The reference focuses on the amount of immunoreactive protein produced by recombinant bacterial cells (see page 1763, left column, " . . . the defect in production of these mutant CT-Bs could occur at any step in the pathway from gene to mature protein"). It is also clear from the description on page 1765 that the focus is to quantify the production of CT-B (see "Assays for CT-B and CT"). It is evident that the assays were not used to examine immune reactivity. This is because the reported method merely uses known amounts of culture extracts rather than known amounts of the recombinant mutant in the assays. Although Jobling may demonstrate that mutations in a sequence might render recombination expression difficult or less effective, the reference does not establish that this is due to the mutation itself. It could be that the mutation may interfere with the correct folding of the proteins in the host cell. However, Jobling does not describe or otherwise indicate that the immune reactivity of the CT-B proteins had they been synthetically produced and subsequently subjected to refolding would be adversely affected.

Finally, Applicant would like to re-emphasize that the claims are not directed to the use of any immunogen derived from OPGL. Rather, the claims are directed to a method of treatment

using an immogen having certain structural and functional features. As discussed above, the immunogenic construct must contain at least one epitope (a preserved OPGL B-cell epitope) and at least one foreign T-helper cell epitope. Although it would be preferable to preserve the overall tertiary structure of the OPGL polypeptide, it is not a requirement. Immunogens not meeting these limitations would not fall within the scope of the claim. The Specification explicitly teaches how to prepare these antigenic polypeptides and use them to down regulate OPGL activity in an animal. Therefore, a person of ordinary skill in the art, after reading the Specification, would recognize that the methods of preparing and selecting modified OPGL polypeptides described therein would yield useful variants to practice the invention.

iii) Paragraph 15

In paragraph 15, the Examiner offers additional comments with respect to the breaking of autotolerance and the unintended result of triggering an autoimmune reaction due to unwarranted cross-reactivity. The Examiner again cites to Bendayan and argues that the use of the constructs as written may trigger rampant and non-specific breaking of auto-tolerance. Applicant refers the Examiner to the arguments presented above and would like to highlight the fact the vaccination technology described in the instant application relies on a polyclonal antibody response. Thus, even if certain single antibody species in the polyclonal serum cross-react with other self-proteins, they would not give rise to a detectable effect. This is because the effect of the immune response is dependent on the cross-reactivity of all of the species present in the polyclonal serum and not just that of a single antibody. In other words, since virtually all antibodies induced will react with the intended self-protein and this will have an effect, it is highly unlikely that a few cross-reactive antibodies will give rise to a detectable effect. The avidity of the induced antibodies will be much, much higher for the binding to OPGL than to any other cross-reacting antigen simply because only a limited amount of the antibodies induced will be capable of cross-reacting.

iv) Paragraphs 16 and 17

In paragraph 16, the Examiner indicates that Applicant's definition of regulation is acceptable. However, the Examiner maintains that the term "analogue" remains an ill-defined concept. Applicant has amended claims to remove this term. In paragraph 17, the Examiner argues that the synthesis, screening and evaluation of muteins of SEQ ID NO. 2 presents an undue burden of experimentation on the skilled artisan with a level of unpredictability. The Examiner cites to Li et al. to argue that the immunogenicity of any given mutein is not guaranteed and must be evaluated with the caveat of possibly triggering an autoimmune reaction beyond what is desired. The Examiner also states that there exists a degree of uncertainty as to whether or not OPGL or its analogues will share immunoreactivity and activity or neither. For these reasons, the Examiner concludes that the claims are not enabled. Applicant respectfully disagrees.

Applicant would like to point out that the purpose of the invention is not to prepare active OPGL polypeptides. Rather, the purpose of the invention is to prepare OPGL analogues (i.e. modified OPGL polypeptides) according to formula I which are then administered to an animal to induce an immune response whereby OPGL activity is down-regulated. The present constructs contain a functional OPBL B-cell epitope and are, therefore, *de facto* immunogens. Applicant agrees that Li et al. demonstrates that point mutations in certain positions in beta-endorphin may lead to a marked reduction/abolition of immune reactivity or physiological activity. However, it is clear from Fig. 2 that the only antibody-binding site of the complete beta-endorphin molecule spans amino acids 11-22. Thus, the abolition of immunoreactivity in Li et al. was due to the deletion of a single amino acid residue within this short segment. The present invention, by contrast, describes constructs whose antibody binding characteristics are preserved. The Examiner has agreed that the instant Specification describes how to prepare, screen and select suitable constructs for use in the invention. One suggested model in the present application is to prepare a panel of variants and select only those that significantly bind a polyclonal antibody that is raised against the wild-type molecule. So, the Specification not only predicts the potential problem described in Li, it also provides several solutions to avoid it (see

paragraph bridging pages 18-19). Accordingly, Applicant submits that the skilled artisan could readily prepare suitable modified OPGL polypeptides for use in the invention.

v) Paragraph 18

Finally in paragraph 18, the Examiner again argues the generation of an immune reaction in response to the adminstration of SEQ ID NO. 2 or other muteins is not assured. The Examiner cites to a study by Münch and Robinson that teaches that the use of endogenous Aß epitopes to trigger an immune response in Alzheimer's patients led to the unintended triggering of an autoimmune response. Applicant is aware of the Münch and Robinson study. This study discusses a number of possible causes for the problems observed in the Elan study. One of possible causes was that "Aß specific activated T-helper cells have the potential to amplify the existing pro-inflammatory conditions that are present in the brains of Alzheimer's disease patients." Other references have focused on the fact that the cause of the neuroinflammatory state can mainly be attributed to the fact that the induced anti-Aß response is exclusively driven by autologous T-helper epitopes meaning that a true, uncontrolled autoimmune state is induced. The present invention, by contrast, relies on foreign T helper cell epitopes. So, the immune response is driven by T helper cells recognizing a foreign element. Consequently, putative cryptic T helper epitopes in the self-protein do not come into play.

One cannot assume that the problems observed in the Elan study could be extrapolated to vaccination against OPGL. The problems in the Elan study merely demonstrate that some targets for immunization are more safe than others. It does not in any way indicate that the type of vaccination described in the instant application would not achieve its goal. It should be pointed out that adverse effects are to be expected with the use of any vaccine or drug. The fact that an adverse effect could be observed has no bearing on whether the invention will work for its intended purpose. The FDA, not the USPTO, is charged with evaluating the toxicity and adverse affects of a particular drug or treatment. A person of ordinary skill would recognize that that the constructs of the invention are immunogenic and will down-regulate OPGL activity in animal. The Specification provides the necessary teaching to prepare and select suitable

constructs for use in the invention. No undue experimentation is required. Accordingly, Applicant submits that claimed invention is fully described and enabled by the Specification.

Favorable consideration and early allowance of the claims is requested.

If the Examiner has any questions concerning this application, the Examiner is requested to contact the undersigned at 714-708-8555 in Costa Mesa, CA.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

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Susan M. Langworthy
(Signature)

Aug. 8, 2003
(Date of Signature)

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PATENT
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IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant:	HALKIER, TORBEN ET AL.	Conf.:	
Appl. No.:	09/396,937	Group: 1647	
Filed:	September 15, 1999	Examiner:	DEBERRY, R.
For:	METHOD FOR DOWN-REGULATING OSTEOPROTEGERIN LIGAND ACTIVITY		

DECLARATION SUBMITTED UNDER 37 C.F.R. §1.132

Assistant Commissioner for Patents
Washington, DC 20231

May 2, 2002

Sir:

I, Marc Hertz, of Gl. Byvej 17, DK-2970 Hørsholm, Denmark do hereby declare the following:

I have attached a copy of my curriculum vitae to this Declaration.

I hold a PhD and am employed as Director of Immunology at Pharmexa A/S in Denmark. I am familiar with the above referenced patent application, as well as the development, use and properties of the anti-OPGL vaccine constructs used in the method of down-regulating osteoprotegerin ligand activity described therein.

I have read and understood the subject matter of the Office Action of December 3, 2001.

The following comments are offered in support of the patentability of the instant invention.

The instant application describes a method of down-regulating osteoprotegerin ligand activity in a host by administering a vaccine against OPGL (RANKL) to treat diseases characterized by excessive bone loss. The overexpression of RANKL has been shown to be involved in the pathogenesis of resorptive bone diseases. In my opinion, the present invention represents a novel approach to treating these types of diseases as it focuses on the down-regulation of RANKL by means of active immunization, a tactic previously untried as persons skilled in the art would not have thought to immunize against a molecule which stimulates T-cell immunity. The present invention's active immunization approach has proven effective in reducing the OPGL activity in animals.

The Examiner has stated that the Specification fails to meet to enablement requirement because it does not describe how to make and use the claimed invention. Specifically, the Examiner noted that the Specification did not (1) teach how to prepare and administer a peptide-based vaccine and (2) demonstrate that administration of the peptide-based vaccine results in *in vivo* down-regulation of OPGL activity or the inducement of an immunological response. I have conducted a number of experiments in mice using the peptide-based vaccines described in the Specification. The peptides were modified in accordance with the teachings on pages 15-29 of the Specification. The formulation and administration of these peptide-based vaccines is generally described on pages 29-36. However in my opinion the preparation of vaccines which contain peptide sequences is well known to persons of skill in the art. The following experimental data demonstrates the effectiveness of the peptide-based vaccine compositions in inducing T-cell proliferation or an immunological response. The results of these experiments were presented at the ASBMR 23rd Annual Meeting in the USA last Fall. Abstracts ("A Novel Therapeutic Vaccine That Prevents Pathological Bone Destruction in Models of Osteoporosis and RA" and "A Therapeutic RANKL Vaccine Induces Nuetralizing Anti-RANKL Antibodies and Prevents Bone Loss in Ovariectomized Mice") of the papers describing the results of the claimed method which were presented at this conference are attached hereto.

The mouse and human RANKL vaccines (hereinafter referred to as "RANKL AutoVac™ constructs) described in the present application and in the Abstracts were tested in vaccination experiments and animal models of pathological bone disease. The RANKL AutoVac™ constructs were designed by incorporating promiscuous T_H epitopes into the TNF-like domain of RANKL. The constructs contained the P2 or P30 T_H epitopes from Tetanus Toxin or the PADRE epitope (licensed from Epimmune) and either the TNF-like domain of mouse RANKL amino acids 158-316 or the TNF-like domain of human RANKL, amino acids 141-317 (see Figure 1).

In the first experiment, murine RANKL AutoVac™ protein was administered to Balb/c mice to determine if immunization with RANKL vaccines prevented or inhibited bone destruction. Vaccinations were administered on days 0, 21, 42 and 63. As seen in Figure 2, immunization with these vaccines resulted in the rapid and sustainable generation of polyclonal anti-RANKL antibodies that cross-react with native non-modified native mouse RANKL. The graph illustrates that the immune response was induced upon vaccination and declined when the vaccinations were halted on day 63.

In a second experiment, we tested the effectiveness of the human RANKL AutoVac™ construct in inducing an immunological response against native, non-modified RANKL proteins. The results of this experiment are summarized in Figure 3. We found that immunoglobulin purified from rat serum from rats immunized with human RANKL AutoVac™ was capable of inhibiting the generation of osteoclasts from MCSF and RANKL-stimulated Balb/c splenocytes and stimulated Balb/c mouse bone marrow cells. The quality of antibodies generated by the murine and human RANKL AutoVac™ was also tested against those generated by non-modified human RANKL protein. As seen in Figure 4, a number of the human and mouse RANKL AutoVac™ proteins induced higher anti-RANKL titres and similar neutralizing titres. The results of this experiment indicate that the antibodies generated by the RANKL AutoVac™ are comparable to those generated by vaccination with the native protein in a xenogenic system.

The effectiveness of the RANKL AutoVac™ constructs on bone resorption was tested in two mouse model studies. The first study simulated post-menopausal osteoporosis where mice were pre-vaccinated with murine RANKL AutoVac™ protein prior to ovariectomy (OVX) surgery (i.e. a surgery which induces bone resorption). The after OVX surgery control mice demonstrated a 16% lower bone mineral bone density compared to the sham-operated control mice. The after OVX surgery mice vaccinated with RANKL AutoVac™ protein did not lose bone after ovariectomy surgery as compared to the sham-operated control mice (see Figure 5). These results indicate that RANKL AutoVac™ is effective in protecting mice from ovariectomy-induced loss of bone mineral density.

The second mouse study was conducted in a model of rheumatoid arthritis. Rheumatoid arthritis is typically characterized by the swelling of the joints, especially small joints. The SKG mouse used in this experiment typically develops rheumatoid arthritis-like symptoms by 8 weeks of age. SKG mice were vaccinated at 2 months and given three subsequent booster vaccinations. We sacrificed the mice at four months of age and conducted a histological examination. We found that immunization with RANKL AutoVac™ protein significantly reduced the recruitment of activated osteoclasts to the joints, reduced bone destruction and reduced synovial inflammation in the subjects (see Figures 6 and 7).

The mouse study experiments described above clearly demonstrate that the RANKL AutoVac™ constructs of the present invention are capable of inducing an immunological response in an animal. Although these studies were conducted in mice, I believe that administering the peptide-based vaccines to humans suffering from rheumatoid arthritis, post-menopausal osteoporosis or other disease characterized by excess bone loss would be equally effective. In my opinion, these experiments clearly demonstrate that the present method can be carried out according to the principles set forth in the Specification without undue experimentation.

I believe that the method of active vaccination against OPGL described in the present application is a feasible and effective way to treat diseases characterized by excessive bone loss.

Contrary to traditional approaches, the inventors have targeted OPGL to reduce OPGL activity in the animal. This is clearly a novel and non-obvious approach of treating these types of diseases. The experiments performed above, which correspond to the method of down-regulating OPGL activity in a mammal described in the Specification, clearly demonstrate that the RANKL AutoVac™ constructs are capable of inducing an immunological response.

The undersigned hereby declares that all statements made herein are based upon knowledge are true, and that all statements based upon information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

DATED: 3 May 2002

Marc Herz

LRS/KR

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail, postage prepaid, in an envelope to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on: Aug 8, 2003
(Date of Deposit)

BIRCH, STEWART, KOLASCH & BIRCH, LLP

Susan M. Langworthy
(Signature)

Aug 8, 2003
(Date of Signature)